PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 401/04, 471/04, 207/08
C07D 207/09, A61K 31/47
A61K 31/435

A1

(11) International Publication Number: WO 92/09597

(43) International Publication Date: 11 June 1992 (11.06.92)

(21) International Application Number: PCT/US91/08422

(22) International Filing Date: 12 November 1991 (12.11.91)

(30) Priority data:
621,101 30 November 1990 (30.11.90) US
730,362 15 July 1991 (15.07.91) US

(71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(72) Inventors: HAGEN, Susan, Elizabeth ; 1035 Paddington Road, Canton Township, MI 48187 (US). SUTO, Mark, James ; 10272 Harpers Ferry Court, Whitmore Lake, MI 48189 (US).

(74) Agents: DAIGNAULT, Ronald, A.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al.

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: OPTICAL ISOMERS OF 7-[3-(1,1-DIALKYLMETHYL-1-AMINO-1-PYRROLIDINYL]-QUINOLONES AND NAPHTHYRIDONES AS ANTIBACTERIAL AGENTS

(57) Abstract

Optically pure isomers of 7-[3-(1,1-dialkylmethyl-1-amino)-1-pyrrolidinyl]-quinolones and naphthyridones as therapeutically active and safe antibacterial agents are described, as well as pharmaceutical compositions thereof, and a method of treating bacterial infections therewith. Also described is a method of manufacture of the quinolones and naphthyridones as well as the starting materials, the optically pure pyrrolidine moieties for attachment at the 7-position.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU+	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE*	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

\+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

OPTICAL ISOMERS OF 7-[3-(1,1-DIALKYLMETHYL-1-AMINO)-1-PYRROLIDINYL]-QUINOLONES AND NAPHTHYRIDONES AS ANTIBACTERIAL AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of United States Application Serial No. 07/621,101, filed November 30, 1990.

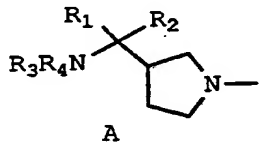
BACKGROUND OF THE INVENTION

The identification and selection of an antibacterial chemotherapeutic agent for development depends on several properties. These include in vitro potency against bacteria, in vivo efficacy in animals and man, pharmacokinetic parameters such as good plasma levels and favorable metabolism, and reduced side effects and toxicity. The ideal agent should have the best blend of these properties.

Within the quinolone/naphthyridone class of antibacterials, efforts are directed toward increasing in vitro and in vivo efficacy while lowering certain side effects such as phototoxicity and cytotoxicity and reducing general toxicity as well.

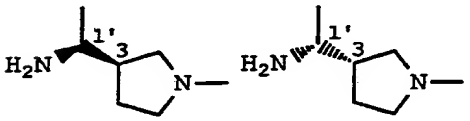
It is also known that within the chiral environment of living organisms, individual stereoisomers/enantiomers of drugs may show unique properties relative to the racemic mixtures. When this occurs, the optimal properties of the drug can only be obtained when the most favorable stereoisomer is utilized in its pure chiral form.

US Patent 4,665,079 shows quinolones and naphthyridines by structural formula to have 7-[3-(1-amino-1-alkylmethyl)-1-pyrrolidinyl] side chains. These compounds of formula A, where R_1 or R_2

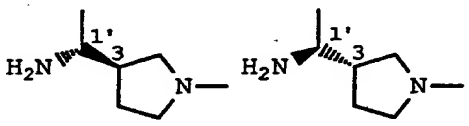


A

are alkyl or hydrogen were revealed to have good in vitro antibacterial potency. European Patent Publication 207,420 describes quinolones/naphthyridones substituted at C_7 with such compounds as A having the two asymmetric centers, and the preparation of two diastereomeric mixtures, each containing two nonseparable enantiomers. These mixtures are now known to consist of the formulas of mixture B and mixture C.



Mixture B

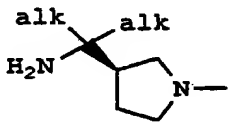


Mixture C

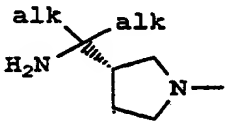
The mixtures B and C (of unknown composition) were described to possess improved in vivo activity relative to unsubstituted compounds (those of formula A where R_1 and R_2 are both hydrogen). All data reported were for the mixtures, and no method of separation of the mixtures was described. At the International Congress of Antimicrobial Agents and Chemotherapy (ICAAC) in Houston, Texas, 1989, there

were reported certain individual enantiomers of 1-ethyl and 1-cyclopropyl-6,8-difluoroquinolone-3-carboxylic acids. The 3-(R)-1'(S) enantiomers were disclosed to have the most potent activity in vitro. One stereoisomer (3R,1'S) was shown to have improved in vivo efficacy relative to an unsubstituted compound (formula A where R_1 and R_2 are both hydrogen). Except for the in vitro data, no other comparisons among the pure stereoisomers were provided.

It has now been found that dialkylation (to be defined below) at the 1'-aminoethyl position of a 3-pyrrolidine substituent removes one asymmetric center and results in a group having only one asymmetric carbon atom and thus only two possible optical isomers instead of four isomers.



R

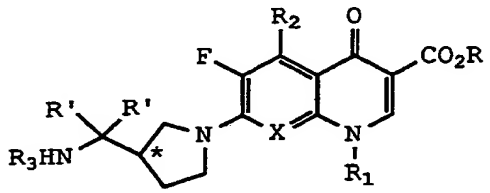


S

It has also been found that the removal of one asymmetric center greatly simplifies the synthesis, separation, and purification relative to pyrrolidine in B and C with two asymmetric centers. It has further been found that the R-(1,1-dialkylated-1-aminomethyl)pyrrolidine, when coupled at the 7-portion of a quinolone or naphthyridone leads to antibacterial agents with improved activity and safety, especially as to cytotoxicity.

SUMMARY OF THE INVENTION

Accordingly, the present invention includes an optical isomer of a compound of the formula I



I

wherein * denotes an asymmetric carbon atom;

X is C-H, C-F, C-Cl, C-CF_3, C-OR" or N, in which R" is hydrogen or alkyl of 1 to 3 carbon atoms;

R is H, alkyl of 1 to 3 carbon atoms or a cation;

R_1 is cyclopropyl or 2,4-difluorophenyl;

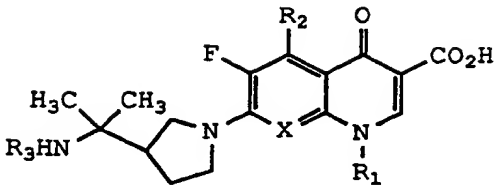
R_2 is hydrogen, methyl or amino;

R_3 is hydrogen, alkyl of 1-3 carbon atoms or an amino protective group;

R' is alkyl of 1 to 3 carbon atoms; or a pharmaceutically acceptable acid addition salt thereof.

The generally preferred isomer has the R configuration.

Preferred R isomers are those of the formula II:



II

wherein R_3 is hydrogen or methyl.

Particularly valuable are the following:

R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

R-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid,

R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

R-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-6-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylic acid,

R-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid,

R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-8-trifluoromethyl-3-quinolinecarboxylic acid,

R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid,

R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

R-5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid,

R-1-cyclopropyl-1,4-dihydro-6-fluoro-8-methoxy-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid,

R-5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid,

R-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid,

R-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-8-trifluoromethyl-3-quinolinecarboxylic acid,

R-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid,

R-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid, and

R-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid,

R-5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid,

R-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid,

R-1-cyclopropyl-8-ethoxy-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid,

R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-ethoxy-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

Certain of the S isomers have their own advantages in terms of reduced cytotoxicity to mammalian cells. The preferred S isomers which are particularly valuable are the following:

S-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

S-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

S-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-6-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylic acid,

S-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid,

S-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid,

S-5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid,

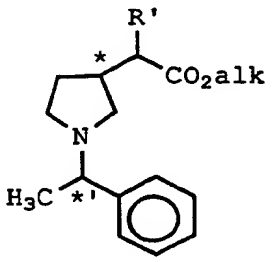
S-5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

The present invention also includes a pharmaceutical composition comprising an antibacterially effective amount of a compound according to formula I in admixture with a pharmaceutically acceptable carrier or diluent.

The present invention further includes a method of treating bacterial infections comprising administering to a host in need thereof a pharmaceutical composition containing a compound of formula I.

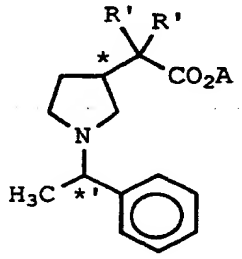
A second aspect of the present invention, includes novel intermediates used to prepare the individual optical isomeric side chains: the [3-(1,1-dialkylated)-1-aminomethylpyrrolidine] as

well as the optically pure side chain itself. These include a compound of the formula



wherein * and *' are asymmetric carbon atoms having either the R or S configuration, and R' and alk are alkyl of 1-3 carbon atoms.

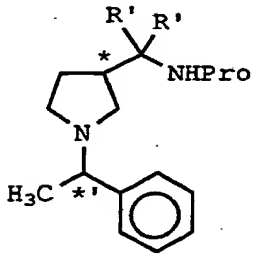
The second aspect also includes a compound of the formula



wherein * and *' are asymmetric carbon atoms having the R or S configurations;

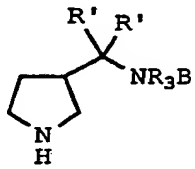
R' is alkyl of 1-3 carbon atoms, and A is hydrogen or alkyl of 1-3 carbon atoms.

The second aspect further includes a compound of the formula



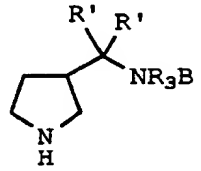
wherein * and *' are asymmetric carbon atoms having the R or S configurations; R' is alkyl of 1-3 carbon atoms, and Pro is an amino protecting group.

The second aspect especially includes the R or S isomer of the formula



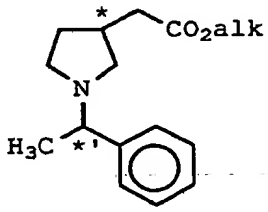
wherein R' is alkyl of 1-3 carbon atoms; R_3 is hydrogen or alkyl of 1-3 carbon atoms; and B is hydrogen or an amino protecting group (Pro).

A third aspect of the present invention is a process for the preparation of the R or S isomer of a compound of the formula



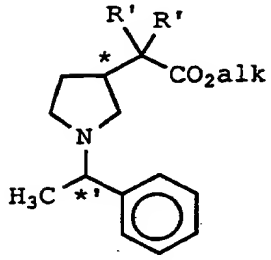
wherein B is a hydrogen or an amino protecting group; R_3 is hydrogen or alkyl from 1-3 carbon atoms, and R' is alkyl of 1-3 carbon atoms, comprising

(a) dialkylating in a step-wise manner a compound of the formula



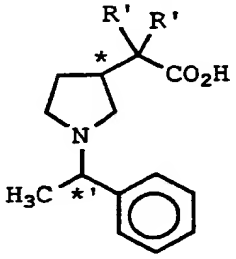
in which alk is alkyl of 1-3 carbon atoms, and * and *' are each either of the R or S configuration and wherein the first alkylation is carried out between about -78° and about -50°C and the second between about -20° and +20°C;

(b) removing the resulting ester (alk) of the formula

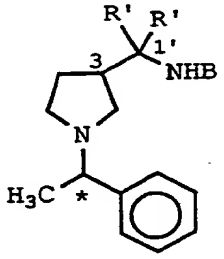


in which R' is alkyl of 1-3 carbon atoms by acid or base hydrolysis;

(c) undergoing the Curtius rearrangement of the resulting acid of the formula

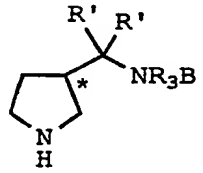


resulting in a compound of the formula



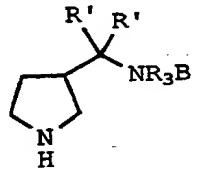
which, if desired, may be alkylated at the 1'-nitrogen by known means;

(d) removing the α-methylbenzyl group from the compound of the previous formula to give the desired product of the formula

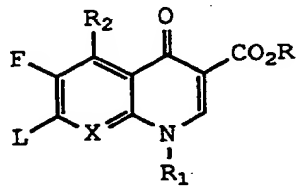


by catalytic hydrogenation.

Finally, the fourth aspect of the present invention is a method of using the R or S isomer of the formula

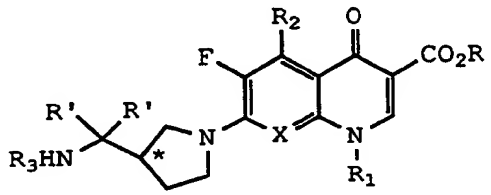


wherein R' is alkyl of 1-3 carbon atoms; R_3 is hydrogen or alkyl of 1-3 carbon atoms, and B is hydrogen or an amino protecting group which comprises reacting said R or S isomer with a compound of the formula



wherein X is C-H, C-F, C-Cl, C-CF_3, C-OR" or N, in which R" is hydrogen or alkyl of 1-3 carbon atoms; R is hydrogen, alkyl of 1-3 carbon atoms or a cation; R_1 is cyclopropyl or 2,4-difluorophenyl; R_2 is

hydrogen, methyl or amino, and L is a leaving group and when B is an amino protecting group, removing said group by known means, e.g., hydrolysis or hydrogenation, to provide an antibacterial compound of the formula



or a pharmaceutically acceptable salt thereof, wherein * is an asymmetric carbon atom having the R or S configuration, and R_3 is hydrogen or alkyl of 1-3 carbon atoms.

DETAILED DESCRIPTION

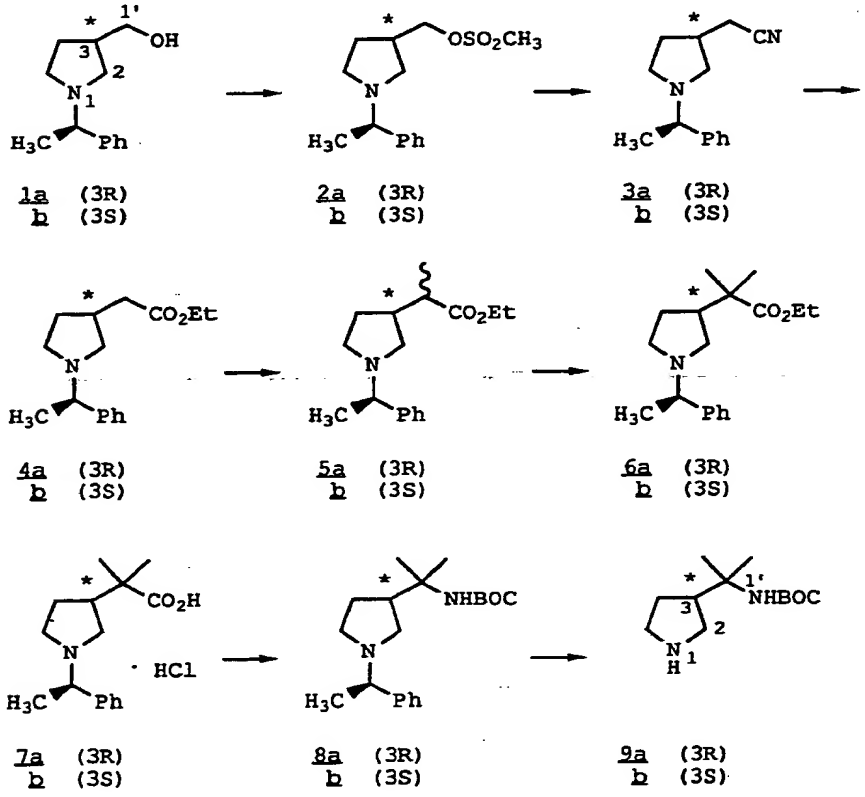
Groups having alkyl of 1 to 3 carbon atoms shown in the formula as R, R', R_3, alk or A includes methyl, ethyl, n-propyl or isopropyl; especially preferred is methyl.

An amino protecting group shown as Pro in the formulae includes known amino protecting groups capable of being removed easily either by hydrolysis or by catalytic hydrogenation. Easily hydrolyzable groups are, for example, t-butoxycarbonyl, carbobenzyloxy, and 4-methoxycarbobenzyloxy, and the like. Especially preferred is the t-butoxycarbonyl group.

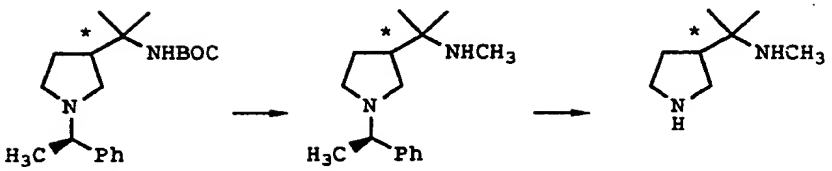
Easily cleavable groups using catalytic hydrogenation, e.g., a noble metal catalyst such as palladium on carbon with hydrogen are, for example, benzyl, α-methylbenzyl, carbobenzyloxy, and the like.

The present invention is especially dependent on the synthesis of optically pure 3-(1,1-dialkylated-1-aminomethyl)pyrrolidines. These can be prepared as illustrated by the following schematic and description.

SCHEME I



SCHEME I (Cont)



8a (3R) b (3S) 10a (3R) b (3S) 11a (3R) b (3S)

Compounds 1a and 1b were prepared essentially as described by Culbertson, et al (J. Med. Chem. 1987;30:1711). The yields were slightly improved particularly for 1b which was obtained in a yield >90%. Compounds 3a and b were reported by L. - Nielsen, et al (J. Med. Chem. 1990;33:71). Compounds 3a and b were obtained in yields of 84% and 57% after bulb to bulb distillation, by proceeding through the methanesulfonate followed by KCN/DMSO.

The esters, compounds 4a and b, were obtained by heating 3a and b in ethanol/H_2SO_4 at reflux.

The desired dialkylated esters 6a and b were obtained via stepwise alkylation of 4a and b. Treatment of 4 at between about -78° to -50°C preferably at about -78°C with lithium diisopropyl amide (LDA) followed by quenching with methyl iodide provided 5. Compound 6 was obtained using LDA once again but performing the reaction at between about

-20° to about +20°C, preferably at about 0°C. Curtius rearrangement using diphenylphosphorylazide and t-butanol provided 8, which was debenzylated under standard conditions, e.g., hydrogen and palladium on carbon catalyst at about room temperature and pressure (50-100 psi) to provide 9. The N-methyl analogues 11a and b were prepared via the lithium aluminum hydride reduction of 8a and b followed by debenzylation under standard conditions.

Proof of stereochemistry was done as described by Culbertson, et al (see above). The schematic diagram illustrates the use of (R)α-methylbenzyl as the protecting group for the pyrrolidine nitrogen as a preferred embodiment. The present invention also includes the use of either the R or S α-methylbenzyl analog and encompasses the use of other chiral protecting groups for the pyrrolidine nitrogen.

The pyrrolidines prepared were coupled to the appropriate quinolone or naphthyridine substrate by published procedures including; Domagala, et al, J. Med. Chem. 1988;31:503, Sanchez, et al, J. Med. Chem. 1988;31:983, Itawa, et al, European Patent Application 8702813.8, 1987, and British Patent 2,011,395A.

The enantiomeric quinolones and naphthyridines of the invention display potent antibacterial activity against gram-negative and especially gram-positive organisms both in vitro as well as in vivo. Their overall therapeutic advantages are also shown by including phototoxicity and cytotoxicity data as compared to a compound described in Example 13 of European Patent Publication 207,420.

The in vitro antibacterial activity is obtained when tested by the microtitration dilution method as

described in Heifetz, et al., Antimicr. Agents & Chemother. 1974;6:124, which is incorporated herein by reference.

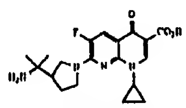
The in vivo activity is obtained when the compounds are tested according to the procedure of Miller, et al (Proc. Soc. Exp. Biol. Med. 1944;57:261). The median protective dose (PD_{50}) was determined in mice given lethal systemic infections. Single doses of compound were given at time of challenge.

The phototoxicity data is obtained using depilated mice. Compound was administered orally each day for four successive days, followed each day by 3 hours of UVA radiation. The mice were examined for any positive signs (redness, erythema) relative to control animals. The no effect dose and the 50% effect dose were determined.

The cytotoxicity data is obtained using hamster V-79 cells. The cells were suspended in tissue culture medium and grown overnight. Cells were treated with drug for 3 hours, washed free of drug and then replated, and the colonies counted after 5 days. The concentration of drug that reduced colonies by 50% relative to control was recorded.

By use of the above methods, the following minimum inhibiting concentration values (MICs in μg/ml), PD_{50}'s in mg/kg, no effect phototoxicity dose in mg/kg and the cytotoxicity IC_{50} in μg/mL were obtained for representative enantiomers of the invention and compounds of the prior art as shown in the table.

The in vivo data as PD_{50}'s are reported below the line of MICs for the same compound.

Example No.	Ent. cloacae MA2646	Esch. coli Vogel	Klebs. pneumoniae MGH-2	Prot. rettgeri M 1771	Pseud. aeruginosa UI-18	Staph. aureus H 228	Staph. aureus UC-76	Strep. faecalis MGH-2	Strep. pneumoniae SV-1	Strep. pyogenes C-203	Photo NED mg/kg	Cytotox µg/mL
3	0.2	0.2 10 3	0.4	0.8	3.1	0.1	0.025	0.1	0.05	0.1 32 7	30	58
4	0.1	0.05 5 1	0.2	0.4	1.6 50 22	0.05	0.003	0.05	0.006 5 2	0.013 4 1	30	130
 Racemic EP0207420 Example 13	0.1	0.1 6 2	0.2	0.4	1.6	0.05	0.013	0.05	0.025 10 3	0.025	30	66

SUBSTITUTE SHEET

Example No.	*Ent. cloacae* MA2646	*Esch. coli* Vogel	*Klebs. pneumoniae* MGH-2	*Prot. rettgeri* M 1771	*Pseud. aeruginosa* UI-18	*Staph. aureus* H 228	*Staph. aureus* UC-76	*Strep. faecalis* MGH-2	*Strep. pneumoniae* SV-1	*Strep. pyogenes* C-203	Photo NED mg/kg	Cytotox µg/mL
1	0.1	0.1 27 4	0.2	0.4	1.6	0.025	0.013	0.05	0.013	0.025 13 4		
2	0.05	0.05 8 1	0.1	0.2	0.8 100 17	0.006	≤0.003	0.013	≤0.003	≤0.003 2 0.14		8
6	0.2	0.2 11 2	0.4	0.4	3.1	0.013	≤0.003	0.025	≤0.003	≤0.003 3 0.5		
7	0.1	0.1 26 3	0.2	0.4	1.6	0.013	≤0.003	0.013	≤0.003	<0.003 3 0.8		18
8	0.2	0.2	0.4	0.8	3.1	0.05	0.013	0.05	0.025	0.025		

Example No.	Ent. cloacae MA2646	Esch. coli Vogel	Klebs. pneumoniae MGH-2	Prot. rettgeri M 1771	Pseud. aeruginosa UI-18	Staph. aureus H 228	Staph. aureus UC-76	Strep. faecalis MGH-2	Strep. pneumoniae SV-1	Strep. pyogenes C-203	Photo NED mg/kg	Cytotox µg/mL
9	0.4	0.4	0.8	0.8	3.1	0.025	0.006	0.05	0.006	0.006 11 2		13
10	0.4	0.4	0.8	1.6	3.1	0.1	0.05	0.4	0.4	0.2		
11	0.1	0.1	0.2	0.4	1.6	0.025	0.013	0.1	0.013	0.013		
12	0.2	0.1	0.2	0.4	1.6	0.025	≤0.003	0.025	0.006	0.006 12 0.6		

The compounds of the invention are capable of forming both pharmaceutically acceptable acid addition and/or base salts. Base salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Also included are heavy metal salts such as for example silver, zinc, cobalt, and cerium. Such heavy metal salts are effective in the treatment of burns especially when applied to the affected surface of a burn victim either directly or in combination with a physiologically acceptable carrier such as a water dispersible, hydrophilic carrier. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine.

Pharmaceutically acceptable acid addition salts are formed with organic and inorganic acids.

Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, gluconic, fumaric, succinic, ascorbic, maleic, methanesulfonic, and the like. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce either a mono or di, etc. salt in the conventional manner. The free base forms may be regenerated by treating the salt form with a base. For example, dilute solutions of aqueous base may be utilized. Dilute aqueous sodium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate solutions are suitable for this purpose. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the

invention. Use of excess base where R' is hydrogen gives the corresponding basic salt.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms and the like are equivalent to the unsolvated forms for purposes of the invention.

The compounds of the invention can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of formula I or a corresponding pharmaceutically acceptable salt of a compound of formula I.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, suppositories, and ointments. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablets disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 or 10 to about 70% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of

the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Such solutions are prepared so as to be acceptable to biological systems (isotonicity, Ph, etc.). Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired. Aqueous suspension suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other well-known suspending agents.

Ointment preparations contain heavy metal salts of a compound of formula I with a physiologically acceptable carrier. The carrier is desirably a conventional water-dispersible hydrophilic or oil-in-water carrier, particularly a conventional semi-soft or cream-like water-dispersible or water soluble, oil-in-water emulsion which may be applied to an affected burn surface or infected surface with a minimum of discomfort. Suitable compositions may be prepared by merely incorporating or homogeneously admixing finely divided compounds with the hydrophilic carrier or base or ointment.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules, powders in vials or ampoules, and ointments in tubes or jars. The unit dosage form can also be a capsule, cachet, tablet, gel or cream itself or it can be the appropriate number of any of these packaged forms.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 100 mg according to the particular application and the potency of the active ingredient.

In therapeutic use as agents for treating bacterial infections, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 3 mg to about 40 mg per kilogram daily. A daily dose range of about 6 mg to about 14 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following examples are illustrative of the present invention.

PREPARATION OF STARTING MATERIALS

Example A

(3R)-1-[(R)-1-Phenylethyl]-3-(cyanomethyl)pyrrolidine

To a solution of (3R)-1-[(R)-1-phenylethyl]-3-(hydroxymethyl)pyrrolidine (25.2 g, 0.12 mol) in CH_2Cl_2 (250 mL) was added Et_3N (18.8 mL, 0.13 mol). The mixture was cooled to 0°C and treated dropwise with methanesulfonyl chloride (10.63 mL, 0.13 mol) dissolved in CH_2Cl_2 (125 mL). The mixture was stirred at 0° for 1.5 hours and then at 25°C for 4 hours. Water was added and the organic layer was separated, washed with $NaHCO_3$ (2X), dried ($MgSO_4$) and concentrated to provide (3R)-1-[(R)-1-phenylethyl]-3-(methanesulfonyl methyl)-pyrrolidine (2a, 33.2 g); NMR ($CDCl_3$) δ 1.39 (m, 3H), 1.54 (m, 1H), 2.0 (m, 1H), 2.3-2.8 (m, 5H), 2.98 (d, 3H), 3.29 (q, 1H), 4.14 (t, 2H), 7.31 (m, 5H). The material was used directly in the next step.

A mixture of 2a (33.2 g, 0.12 mol) in DMSO (500 mL) was treated with KCN (16 g, 0.24 mol) and heated at 135-140° for 18 hours. The reaction was cooled, poured into water (1600 mL) and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated. The residue was distilled (bulb to bulb) to provide the desired compound 3a (22.0 g, 84%); bp 40-50°, 0.2 mm; NMR ($CDCl_3$) δ 1.35 (d, 3H), 1.40 (m, 1H), 2.0-2.8 (m, 9H), 3.1 (q, 1H), 7.2 (m, 5H); Analysis ($C_{14}H_{18}N_2$);
Calcd.: C, 78.46; H, 8.47; N, 13.07.
Found: C, 78.56, H, 8.41; N, 12.56.

Example B

Ethyl (3R)-1-[(R)-1-phenylethyl)pyrrolidine-3-acetate; 4a

To a mixture of EtOH (30 mL) and H_2SO_4 (15 mL) at 25°C was added (3R)-1-[(R)-1-phenylethyl]-3-(cyanomethyl)pyrrolidine 3a (7.5 g, 35 mmol) in EtOH

(5 mL). The solution was heated at reflux for 7 hours, cooled, and the volume reduced by approximately one-half under reduced pressure. The residue was made basic with NaOH and extracted with EtOAc. The organic layer was dried, concentrated, and the residue distilled (bulb to bulb) to provide 4a (6.7 g, 73%); bp 120-130°C (0.1-0.2 mm).

Example C

(3S)-1-[(R)-1-phenylethyl]-3-(cyanomethyl)pyrrolidine (3b)

This was prepared in a manner similar to 3a (Example A) in a yield of 57%; bp 110-120°C (0.3-0.4 mm bulb to bulb).

Example D

Ethyl (3S)-1-[(R)-1-phenylethyl]pyrrolidine-3-acetate (4b)

This was prepared in a manner similar to 4a (Example B) in a yield of 78%; bp 120-130° (0.025 mm).

Example E

Ethyl (3R)-1-[(R)-1-phenylethyl]-pyrrolidine-3-(2-propionate) (5a)

To a solution of LDA (11.3 mmol) in THF (30 mL) at -78°C was added a solution of (3R)-ethyl-1-[(R)-1-phenylethyl)pyrrolidine-3-acetate (4a) in THF (15 mL). The reaction was stirred at -78°C for 45 minutes and methyl iodide (1.0 mL, 16.1 mmol) was added. The reaction was allowed to warm to 25°C and stirring was continued for 1 hour. It was poured into saturated NH_4Cl and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated. The residue was filtered through silica gel (EtOAc) and the filtrates were concentrated to provide 5a (2.29 g, 91%); NMR ($CDCl_3$) δ 1.10-1.29 (m, 6H), 1.38 (d, 3H), 1.48 (m, 1H),

1.96 (m, 1H), 2.15 (m, 1H), 2.35-2.50 (m, 4H), 2.87 (m, 1H), 3.24 (m, 1H), 4.10 (q, 2H), 7.30 M, 5H); MS (M+1) = 276.

Example F

Ethyl (3R)-1-[(R)-phenylethyl]pyrrolidine-3-[2-(2-methyl-propionate)] (6a)

To a solution of LDA (25.2 mmol) in THF (50 mL) cooled to -78°C was added a solution of ethyl (3R)-1-[(R)-phenylethyl]pyrrolidine-3-(2-propionate) in THF (50 mL) dropwise. After the addition was complete the reaction was warmed to 0°C and stirred for 90 minutes. Then methyl iodide (2.6 mL, 41.8 mmol) was added, the mixture was allowed to warm to room temperature and stirred for 2 hours. The resulting suspension was poured into saturated NH_4Cl and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated to an oil. Chromatography over silica gel (9/1, $CHCl_3$/EtOAc) provided 6a (2.0 g, 83%); NMR ($CDCl_3$) δ 1.12 (d, 6H), 1.27 (t, 3H), 1.37 (d, 3H), 1.60 (m, 1H), 1.80 (m, 1H), 2.20 (m, 1H), 2.40-2.60 (m, 3H), 2.75 (m, 1H), 3.10 (m, 1H), 4.08 (q, 2H), 7.30 (m, 5H); MS (M+1) = 290.

Example G

Ethyl (3S)-1[(R)-1-phenylethyl]pyrrolidine-3-(2-propionate) (5b)

This was prepared in a yield of 87% in a manner analogous to 5a (Example E). The material was purified by chromatography over silica gel (9/1; $CHCl_3$/EtOH); MS (M+1) = 276.

Example H

(3S)-Ethyl-1[(R)-1-phenylethyl]pyrrolidine-3-[2-(2-methylpropionate)] (6b)

This was prepared in a yield of 92% in a manner analogous to 6a (Example F); NMR ($CDCl_3$) δ 1.11 (s, 6H), 1.20 (5, 3H), 1.34 (d, 3H), 1.84 (m, 1H), 2.30 (m, 2H), 2.48 (m, 2H), 2.74 (m, 1H), 3.15 (q, 1H), 4.08 (q, 2H), 7.30 (m, 5H); MS (M+1) = 290.

Example I

(3R)-1-[(R)-1-phenylethyl]pyrrolidine-3-[2-(2-methyl-propionic acid)] monohydrochloride (7a)

A solution of (3R)-ethyl-1-[(R)-1-phenylethyl]-pyrrolidine-3-[2-(methylpropionate)] (6a) in THF (3 mL) and 6M HCl (40 mL) was refluxed for 4 hours and then stirred at room temperature for 18 hours. The aqueous solution was washed with ether and then concentrated to a foam to provide 6a which was used directly in the next step; NMR ($CDCl_3$) δ 1.05 (m, 6H), 1.12 (s, 3H), 1.62 (m, 3H), 2.67-3.20 (m, 3H), 1.7-2.1 (m, 2H), 3.75 (m, 1H), 4.44 (m, 1H), 7.43 (m, 3H), 7.65 (m, 2H).

Example J

(3R)-(1'-Methyl)-1'-t-butoxycarbonylaminoethyl)-1-[(R)-1-phenylethyl]pyrrolidine (8a)

To a solution of (3R)-1-[(R)-1-phenylethyl]-pyrrolidine-3-[-2-(2-methylpropionic acid)] monohydrochloride (7a) (3.50 g, 11.8 mmol) in t-butanol (180 mL) was added Et_3N (2.38 g, 23.6 mmol). The mixture was stirred at room temperature for 1 hour and then diphenylphosphoryl azide (2.5 mL, 11.6 mmol) was added dropwise. The mixture was refluxed for 18 hours, cooled, and concentrated. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated to an oil. Chromatography over silica gel ($CHCl_3$/EtOAc 8/2)

provided the desired 8a (1.8 g, 47%); NMR ($CDCl_3$) δ 1.18 (m, 3H), 1.27 (m, 3H), 1.35 (d, 3H), 1.48 (s, 9H), 1.86 (m, 2H), 2.15 (m, 3H), 2.56 (m, 1H), 3.12 (m, 2H), 7.33 (m, 5H); MS (M+1) = 333.

Example K

(3R)-(1'-Methyl-1'-t-butoxycarbonylaminoethyl)-pyrrolidine (9a)

A solution of (3R)-(1'-methyl-1'-t-butoxycarbonyl-aminoethyl)-1-[(R)-1-phenylethyl]pyrrolidine (8a) (0.43 g, 1.29 mmol), 20% Pd/C (0.25 g) and methanol was shaken in a hydrogen atmosphere for 21 hours. The catalyst was filtered through celite and the filtrate was concentrated to provide 9a (0.25 g, 86%) as an oil; NMR ($CDCl_3$) δ 1.21 (d, 6H), 1.42 (s, 9H), 1.60-2.01 (m, 3H), 2.71-3.30 (m, 4H).

Example L

(3S)-1-[(1R)-Phenylethyl]pyrrolidine-3[-2-(2-methyl-propionic acid)] monohydrochloride (7b)

This was prepared in an analogous manner to 7a (Example I) in a yield of ~98%; NMR ($CDCl_3$) δ 1.03 (d, 6H), 1.62 (d, 3H), 1.90 (m, 2H), 2.81 (m, 2H), 3.73 (m, 1H), 4.40 (m, 1H), 7.43 (m, 3H), 7.62 (m, 2H).

Example M

(3S)-1'-Methyl-1'-t-butoxycarbonylaminoethyl)-1-[(R)-1-phenylethyl]pyrrolidine (8b)

This was prepared in a manner analogous to 8a (Example J) in a yield of 53%; NMR ($CDCl_3$) δ 1.29 (d, 6H), 1.27 (s, 9H), 2.20-2.70 (m, 5H), 3.27-5.80 (m, 2H), 4.01 (m, 1H), 7.32 (m, 5H).

Example N

(3S)-(1'-Methyl-1'-t-butoxycarbonylaminoethyl)-pyrrolidine (9b)

This was prepared in a manner analogous to 9a in Example K. A yield of 96%; NMR ($CDCl_3$) δ 1.14 (d, 3H), 1.30 (d, 3H), 1.42 (s, 9H), 1.75 (m, 1H), 1.94 (m, 1H), 2.82-3.35 (m, 4H), 3.60 (m, 1H), 4.0 (bs, 2H).

Example O

(3R)-1'-Methyl-1'-methylaminoethyl)-1-[(R)-1-phenylethyl]pyrrolidine (10a)

To a solution of 1.0 g (3.0 mmol) of (3R)-(1'-methyl-1'-t-butoxycarbonylaminoethyl)-1-[(R)-1-phenylethyl]pyrrolidine (8a) in 50 mL of dry THF was added 1.14 g (30.0 mmol) of lithium aluminum hydride portionwise. The reaction mixture was refluxed for 90 minutes, then cooled to room temperature. The mixture was treated with 0.9 mL of water, 1.2 mL of 40% NaOH, and 4.2 mL of water. The solids were filtered and washed with ether, and the combined filtrate and washings were concentrated. The product was distilled (bulb to bulb) to give the title compound (0.62 g, 84%); bp 100-110°C, 0.2 mm; NMR ($CDCl_3$) δ 0.95 (d, J=5.0Hz, 6H), 1.35 (d, J=6.7Hz, 3H), 1.5-1.8 (m, 4H), 2.2 (m, 2H), 2.3 (s, 3H), 2.5 (t, 1H), 2.8 (m, 1H), 3.2 (q, 1H), 7.3 (m, 5H).

Example P

(3R)-(1'-Methyl-1'-methylaminoethyl)pyrrolidine (11a)

A solution of 0.51 g (2.1 mmol) of (3R)-(1'-methyl-1'-methylaminoethyl)-1-[(R)-1-phenylethyl]pyrrolidine (10a), 0.5 g of 20% Pd/C, and 100 mL of methanol was shaken in a hydrogen atmosphere for 19 hours. The catalyst was filtered through celite and the filtrate was concentrated to give 0.28 g (96%) of the title compound as a clear yellow oil; NMR ($CDCl_3$) δ 1.05 (d,

J=2Hz, 6H), 1.7 (m, 2H), 1.85 (m, 1H), 2.3 (s, 3H), 2.8 (t, 1H), 3.0 (m, 3H), 3.65 (bs, 2H).

Example 1

(S)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, monohydrochloride

A solution of 0.70 g (3.07 mmol) of (3S)-(1'-methyl-1'-t-butoxycarbonylaminoethyl)-pyrrolidine (9b), 0.66 g (2.20 mmol) of 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.72 g (7.2 mmol) of triethylamine and 30 mL of acetonitrile was heated at reflux for 6 hours. The solvent was removed in vacuo and the residue was chromatographed on E. Merck silica gel (230-400 mesh) eluting with $CHCl_3$/MeOH (90:10) to give 0.95 g of the (S)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid as a yellow powder. NMR (DMSO-d_6); δ 8.80 (s, 1H), 7.83 (d, 1H), 6.6 (bs, 1H), 4.35 (m, 1H), 3.65-3.90 (m, 2H), 3.50 (m, 1H), 3.35 (m, 1H), 2.95 (m, 1H), 2.0 (m, 1H), 1.8 (m, 1H), 1.38 (s, 9H), 1.25 (d, 6H), 1.02-1.28 (m, 4H).

A solution of 0.96 g (1.87 mmol) of the above compound in 5 mL of glacial acetic acid and 5 mL of 6.0 M hydrochloric acid was stirred at room temperature for 2 hours and concentrated in vacuo. The residue was triturated with 20 mL of 2-propanol/ether (1:5) and the resulting solid was removed by filtration, washed with ether, and dried in vacuo to give 0.73 g of the title compound as a bright yellow solid, mp 220-223°C.

Example 2

(R)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, monohydrochloride

A solution of 0.71 g (2.37 mmol) of 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.70 g (3.07 mmol) of (3R)-(1'-methyl-1'-t-butoxycarbonylaminoethyl)pyrrolidine (9a), 0.72 g (7.2 mmol) of triethylamine and 20 mL of acetonitrile was heated at reflux for 7 hours. The solvent was removed in vacuo and the residue was chromatographed on E. Merck silica gel (230-400 mesh) eluting with $CHCl_3$/EtOH (90;10) to give 1.1 g of (R)-7-[3-(1-t-Butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid as a yellow powder. NMR (DMSO-d_6); δ 8.79 (s, 1H), 7.82 (d, 1H), 4.36 (m, 1H), 3.84 (m, 1H), 3.72 (m, 1H), 3.51 (m, 1H), 3.38 (m, 1H), 2.88 (m, 1H), 1.91 (m, 1H), 1.75 (m, 1H), 1.37 (s, 9H), 1.25 (d, 6H), 0.88-1.22 (m, 4H).

A slurry of 1.04 g (2.05 mmol) of the above compound in 5 mL of tetrahydrofuran was treated portionwise with 3 mL of 12.0 M hydrochloric acid (1/2 mL every 15 minutes) over 1.5 hours. The resulting solution was stirred at room temperature for an additional 1.5 hours and the solvent was removed in vacuo. The oily residue was triturated with 20 mL of 2-propanol/ether (1:5) and the resulting solid was removed by filtration, dissolved in water, filtered through a fiber glass pad to clarify, and lyophilized. The fluffy solid was filtered with the aid of 10 mL of acetonitrile, washed with ether, and dried in vacuo to give 0.56 g of the title compound, mp 225-227°C.

Example 3

(S)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monohydrochloride

A solution of 0.39 g (1.39 mmol) of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 0.35 g (1.53 mmol) of (3S)-(1'-methyl-1'-t-butoxycarbonylaminoethyl)-pyrrolidine (9b), 0.46 g (4.6 mmol) of triethylamine and 20 mL of acetonitrile was stirred at reflux for 18 hours. The reaction mixture was cooled to 0°C and the solid was removed by filtration, washed with acetonitrile, ether, and dried in vacuo to give 1.13 g of a white solid. The filtrate was concentrated to give an additional 0.95 g of white solid. The combined solids were chromatographed on E. Merck silica gel (230-400 mesh), eluting with $CHCl_3$/MeOH (90:10) to give 1.76 g of (S)-7-[3-(t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid; NMR (DMSO-d_6); δ 8.55 (s, 1H), 7.95 (d, 1H), 6.7 (bs, 1H), 3.51-4.20 (m, 3H), 2.95-3.11 (m, 3H), 2.0 (m, 1H), 1.9 (m, 1H), 1.17-1.37 (m, 19H).

A solution of 0.78 g (1.64 mmol) of the above compound in 10 mL of glacial acetic acid and 15 mL of 6.0 M hydrochloric acid was stirred at room temperature for 18 hours. The solvent was removed in vacuo and the golden, oily residue was triturated with 20 mL of 2-propanol/ether (1:4). The solid which developed was removed by filtration, washed with acetonitrile, ether, and dried in vacuo to give 0.51 g of the title compound, mp 280-282°C.

Example 4

(R)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monohydrochloride

A solution of 1.24 g (4.39 mmol) of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 1.2 g (5.25 mmol) of (3R)-(1'-methyl-1'-t-butoxycarbonylaminoethyl)-pyrrolidine (9a), 1.33 g (13.2 mmol) of triethylamine and 35 mL of acetonitrile was heated at reflux for 18 hours. The solvent was removed in vacuo and the residue was chromatographed on E. Merck silica gel (230-400 mesh), eluting with $CHCl_3$/MeOH (90:10) to give 1.61 g of (R)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid. NMR (DMSO-d_6); δ 8.55 (s, 1H), 7.93 (d, 1H), 3.6-4.05 (m, 5H), 2.9 (m, 1H), 2.05 (m, 1H), 1.85 (m, 1H), 1.39 (s, 9H), 1.10-1.31 (m, 10H).

A suspension of 1.50 g (3.16 mmol) of the above compound in 20 mL of 6.0 M hydrochloric acid and 20 mL of glacial acetic acid was stirred at room temperature for 18 hours. The resulting solution was filtered through a fiber glass pad to clarify and the filtrate was concentrated in vacuo to a golden oil. The residue was triturated with 30 mL of 2-propanol/ether (1:5) and the resulting solid was removed by filtration, washed with ether, and dried in vacuo to give 0.95 g of the title compound. NMR (DMSO-d_6); δ 8.58 (s, 1H), 8.15 (bs, 2H), 8.0 (d, 1H), 3.6-4.1 (m, 5H), 2.55 (m, 1H), 2.1 (m, 1H), 1.9 (m, 1H), 1.32 (s, 6H), 1.05-1.2 (m, 4H).

Example 5

(R)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, monohydrochloride

A solution of 0.62 g (2.34 mmol) of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.75 g (3.28 mmol) of (3R)-(1'-methyl-1'-t-butoxycarbonylaminoethyl)pyrrolidine (9a), 0.72 g (7.2 mmol) of triethylamine and 30 mL of acetonitrile was heated at reflux for 18 hours. The suspension was cooled to 0°C and the solid was removed by filtration, washed with water, acetonitrile, ether, and dried in vacuo to give 0.62 g of (R)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, which was used without further purification.

A solution of 0.61 g (1.29 mmol) of the above compound in 5 mL of 6.0 M hydrochloric acid and 5 mL of glacial acetic acid was stirred at room temperature for 3.5 hours. The solution was concentrated to a greenish-yellow oil which was triturated with 20 mL of 2-propanol/ether (1:3) to give 0.42 g of the title compound as a bright yellow solid. NMR (DMSO-d_6); δ 8.44 (s, 1H), 7.53 (s, 1H), 6.91 (d, 1H), 3.40-3.62 (m, 5H), 2.83 (m, 1H), 1.96 (m, 2H), 1.30-1.35 (d, 6H), 1.05-1.12 (m, 4H).

Example 6

(R)-8-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-{3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl}-4-oxo-3-quinolinecarboxylic acid, monohydrochloride

A solution of 0.42 g (1.40 mmol) of 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.27 g (1.90 mmol) of (3R)-(1'-methyl-1'-methylaminoethyl)pyrrolidine (11a),

0.43 g (4.3 mmol) of triethylamine and 50 mL of acetonitrile was heated at reflux for 32 hours. The reaction was concentrated in vacuo and the residue was suspended in water. The pH was adjusted to 12.0 and the solution was filtered through a fiber glass pad to clarify. The filtrate was acidified to pH 2.0 with 6.0 M hydrochloric acid, filtered, and the filtrate lyophilized. The residue was suspended in 10 mL of 12.0 M hydrochloric acid and filtered. The filtrate was concentrated in vacuo and the residue was removed by filtration, washed with 2-propanol, ether, and dried in vacuo to give 0.22 g of the title compound, mp 270-273°C.

Example 7

(R)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

A solution of 0.60 g (1.75 mmol) of the borate ester of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (European Patent Publication No. 0 241 206), 0.52 g (2.28 mmol) of (3R)-(1'-methyl-1'-t-butoxycarbonyl-aminoethyl)pyrrolidine (9a), 0.68 g (5.26 mmol) of diisopropylethylamine, and 50 mL of acetonitrile was stirred at room temperature for 3 days. The solution was concentrated to an orange solid which was dissolved in 50 mL of ethanol, treated with 5 mL of triethylamine, and heated at reflux for 5 hours. The solution was cooled to room temperature and concentrated. The residue was chromatographed on E. Merck silica gel (230-400 mesh), eluting with 90:10 $CHCl_3$·MeOH to give 0.84 g of (R)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid, mp 70-72°C; NMR ($CDCl_3$) δ 8.77 (s, 1H), 7.78 (d,

J=13.8 Hz, 1H), 4.7 (bd, 1H), 4.00 (m, 1H), 3.85 (m, 1H), 3.60 (m, 6H), 3.00 (m, 1H), 2.05 (m, 1H), 1.78 (m, 1H), 1.42 (m, 17H), 1.12 (m, 1H), 0.86 (m, 1H).

A solution of 0.84 g (1.67 mmol) of the above compound in 5 mL of THF and 10 mL of 6.0 M hydrochloric acid was heated at reflux for 18 hours. The solvent was evaporated in vacuo, and the residue was triturated with 30 mL of 2-propanol:ether (1:10). The solids that developed were filtered, washed with ether, and dried in vacuo to give 0.36 g of the title compound as the hydrochloride salt; mp 225-227°C.

Example 8

(S)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

A solution of 0.60 g (1.75 mmol) of the borate ester of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid, 0.52 g (2.28 mmol) of (3S)-(1'-methyl-1'-t-butoxycarbonyl-aminoethyl)pyrrolidine (9b), 0.68 g of diisopropylethylamine, and 30 mL of acetonitrile was stirred at room temperature for 3 days. The solution was concentrated to a yellow solid which was dissolved in 50 mL of ethanol, treated with 5 mL of triethylamine, and heated at reflux for 6 hours. The solution was cooled to room temperature and concentrated. The residue was chromatographed on E. Merck silica gel (230-400 mesh), eluting with 90:10 $CHCl_3$:MeOH, to give 0.57 g of (S)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid; NMR ($CDCl_3$) δ 15.0 (bs, 1H), 8.80 (s, 1H), 7.80 (d, J=14 Hz, 1H), 4.55 (bs, 1H), 4.00 (m, 1H), 3.82 (m, 1H), 3.68 (m, 1H), 3.45 (m, 2H), 3.56 (s, 3H), 3.0 (m, 1H), 2.03 (m,

1H), 1.78 (m, 1H), 1.40 (m, 17H), 1.10 (m, 1H), 0.86 (m, 1H).

A solution of 0.56 g (1.11 mmol) of the above compound in 5 mL of THF and 30 mL of 6.0 M hydrochloric acid was heated at reflux for 1 hour and stirred at room temperature for 18 hours. The solvent was evaporated in vacuo, and the residue was triturated with 30 mL of 2-propanol:ether (1:10). The solids that formed were filtered, washed with ether, and dried to give 0.48 g of the title compound as the hydrochloride salt; mp 228-230°C.

Example 9

(R)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A suspension of 0.56 g (2.0 mmol) of 5-amino-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.60 g (2.6 mmol) of (3R)-(1'-methyl-1'-t-butoxycarbonylaminoethyl)pyrrolidine (9a), 0.81 g (8.0 mmol) of triethylamine, and 30 mL of pyridine was heated at reflux for 18 hours. The solution was cooled to room temperature and concentrated to a brown foam. The residue was chromatographed on E. Merck silica gel (230-400 mesh), eluting with 90:10 $CHCl_3$:MeOH to give 1.0 g of (R)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. NMR ($CDCl_3$) δ 8.55 (s, 1H), 6.45 (bs, 2H), 6.21 (d, J=7.0 Hz, 1H), 3.7-3.4 (m, 4H), 3.35 (m, 1H), 3.00 (m, 1H), 2.04 (m, 1H), 1.95 (m, 1H), 1.44 (m, 17H), 1.09 (m, 2H). Contained a trace of pyridine.

A solution of 1.00 g (2.0 mmol) of the above compound was dissolved in 10 mL of THF and 15 mL of 6.0 M hydrochloric acid and heated at reflux for

20 minutes. The solution was cooled and concentrated in vacuo. The residue was triturated with 30 ml of 2-propanol:ether (1:10), and the solids that formed were filtered, washed with ether and chloroform, and dried to give 0.51 g of the title compound as a yellow powder; mp >300°C.

Example 10

(R)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid

A solution of 0.92 g (2.62 mmol) of 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid, 0.90 g (3.9 mmol) of (3R)-(1'-methyl-1'-t-butoxycarbonyl-aminoethyl)pyrrolidine (9a), 0.80 g (7.9 mmol) of triethylamine, and 50 mL of acetonitrile was heated at reflux for 18 hours. The solution was cooled to room temperature and concentrated in vacuo to an orange solid. The residue was chromatographed on E. Merck silica gel (230-400 mesh), eluting with 90:10 $CHCl_3$:MeOH to give 1.47 g of (R)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid; NMR ($CDCl_3$) δ 8.47 (s, 1H), 7.44 (m, 1H), 7.15 (m, 2H), 5.64 (d, J=7HZ, 1H), 4.47 (bs, 1H), 3.50-3.20 (m, 4H), 2.85 (d, J=3.5HZ, 3H), 1.91 (m, 1H), 1.74 (m, 2H), 1.42 (s, 9H), 1.29 (d, J=11HZ, 6H).

A solution of 1.47 g (2.62 mmol) of the above compound in 30 mL of 6M hydrochloric acid was heated at reflux for 1 hour, then cooled to room temperature. The solution was concentrated to an orange oil which was dissolved in water, filtered through a fiberglass pad, and neutralized to pH 7.2. The solids that formed were filtered, washed with water and ether, and dried in

vacuo to give 0.34 g of the title compound; mp 156-158°C.

Example 11

(S)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid

A solution of 0.51 g (1.45 mmol) of 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid, 0.46 g (2.00 mmole) of (3S)-(1'-methyl-1'-t-butoxycarbonyl-aminoethyl)pyrrolidine (9b), 0.44 g (4.36 mmol) of triethylamine, and 20 mL of acetonitrile was heated at reflux for 12 hours. The solution was cooled and concentrated to a tan solid. The residue was chromatographed on E. Merck silica gel (230-400 mesh), eluting with 90:10 $CHCl_3$:MeOH, to give 0.69 g of (S)-7-[3-(1-N-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid; NMR ($CDCl_3$) δ 8.47 (s, 1H), 7.44 (m, 1H), 7.15 (m, 2H), 5.64 (d, J=7.2 Hz, 1H), 4.47 (bs, 1H), 3.5-3.2 (m, 4H), 2.85 (d, J=3.5 Hz, 3H), 1.91 (m, 1H), 1.74 (m, 2H), 1.42 (s, 9H), 1.29 (d, J=11 Hz, 6H).

A solution of 0.60 g (1.07 mmol) of the above compound in 10 mL of THF and 20 mL of 60 M hydrochloric acid was heated at reflux for 2 hours and then stirred at room temperature for 18 hours. The solution was concentrated in vacuo, and the residue was triturated with 30 ml of 2-propanol:ether (1:10). The solids that formed were filtered, washed with ether, and dried in vacuo to give 0.41 g of the title compound as the hydrochloride salt; mp 244-246°C.

Example 12

(S)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A solution of 0.41 g (1.45 mmol) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.46 g (2.00 mmol) of (3S)-(1'-methyl-1'-t-butoxycarbonylaminoethyl)pyrrolidine (9b), 0.44 g (4.36 mmol) of triethylamine, and 25 mL of acetonitrile was heated at reflux for 18 hours. The mixture was cooled to 5°C, and the solids were filtered, washed with water and ether, and dried in vacuo to give 0.47 g of (S)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid; NMR (DMSO-d_6) δ 8.63 (s, 1H), 7.73 (d, J=13.5 Hz, 1H), 6.64 (bs, 1H), 4.10 (m, 1H), 3.85 (m, 1H), 3.70 (m, 1H), 3.54 (m, 1H), 3.35 (m, 1H), 2.80 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.40 (bs, 9H), 1.26 (d, 8H), 1.17 (m, 2H).

A solution of 0.40 g (0.8 mmol) of the above compound in 5 mL of THF and 25 mL of 6.0 M hydrochloric acid was stirred at room temperature for 3 days. The solvent was evaporated in vacuo, and the oily residue was triturated with 30 ml of 2-propanol. The solids that formed were filtered, washed with 2-propanol and ether, and dried in vacuo to give 0.29 g of the title compound as the hydrochloride salt; mp 261-264°C.

EXAMPLE 13

(R)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monohydrochloride

A solution of 0.55 g (1.56 mmol) of 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 0.45 g (1.70 mmol) of (3R)-(1'-methyl-1'-t-butoxycarbonylaminoethyl)-

pyrrolidine (9a), 0.95 g (9.4 mmol) of triethylamine and 40 ml of acetonitrile was heated at reflux for 90 minutes. The solvent was removed in vacuo to provide 1.3 g of (R)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, which was used without further purification.

A solution of 1.3 g of the above compound in 30 ml of methylene chloride was treated with HCl(g) for 3 minutes. The mixture was stirred for 18 hours and concentrated. The resulting residue was crystallized from ethanol-water to provide 0.38 g of the desired product; mp >250°C (dec); NMR (DMSO-d_6) δ 1.20 (s, 6H), 1.80 (m, 1H), 1.93 (m, 1H), 2.45 (m, 1H), 3.90-4.11 (m, 4H), 7.41 (m, 1H), 7.60 (m, 1H), 7.86 (m, 1H), 8.13 (d, 1H), 8.26 (bs, 3H), 8.72 (s, 1H).

EXAMPLE 14

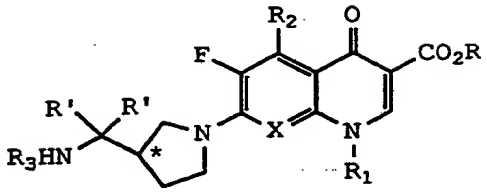
(R)-7-[3-(1-Amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-ethoxy-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, monohydrochloride

A solution of 0.51 g (1.40 mmol) of the borate ester of 1-cyclopropyl-6,7-difluoro-8-ethoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.45 g (1.7 mmol) of (3R)-(1'-methyl-1'-t-butoxycarbonyl-aminoethyl)pyrrolidine (9a), 0.71 g (5.6 mmol) of diisopropylamine and 30 ml of acetonitrile was stirred at room temperature for 16 hours. The mixture was concentrated to an oil which was dissolved in 50 ml of ethanol and 5 ml of triethylamine. The mixture was heated at reflux for 2 hours, cooled and concentrated to afford 0.76 g of (R)-7-[3-(1-t-butoxycarbonylamino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-ethoxy-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid, which was used without further purification.

A solution of 0.76 g of the above compound in 30 ml of CH_2Cl_2 was treated with HCl(g) for 3 minutes. The mixture was stirred at room temperature for 18 hours, concentrated, and the resulting residue crystallized from methanol-H_2O to provide 0.38 g of the desired product; mp 210°C (dec); NMR (DMSO-d_6) 0.89 (m, 1H), 1.06 (m, 2H), 1.21 (m, 1H), 1.27 (t, 3H), 1.33 (s, 6H), 1.82 (m, 1H), 2.09 (m, 1H), 2.55 (m, 1H), 3.54 (m, 2H), 3.65 (q, 2H), 3.80 (m, 2H), 4.14 (m, 1H), 7.67 (d, 1H), 8.25 (bs, 3H), 8.68 (s, 1H).

CLAIMS

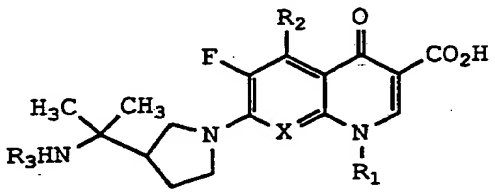
1. An optical isomer of a compound of the formula



wherein * denotes an asymmetric carbon atom;
X is C-H, C-F, C-Cl, C-CF_3, C-OR" or N, in which R" is hydrogen or alkyl of 1 to 3 carbon atoms, or a pharmaceutically acceptable acid addition salt thereof;
R is H, alkyl of 1 to 3 carbon atoms or a cation;
R_1 is cyclopropyl or 2,4-difluorophenyl;
R_2 is hydrogen, methyl or amino;
R_3 is hydrogen, alkyl of 1-3 carbon atoms or an amino protective group;
R' is alkyl of 1 to 3 carbon atoms.

2. The optical isomer of Claim 1, wherein * is of the R configuration.

3. The R isomer of Claim 2, and of the formula



wherein R_3 is hydrogen or methyl.

4. The R isomer of Claim 3, wherein X is C-H, C-F, C-Cl, C-CF_3, C-OCH_3, C-OCH_2CH_3, or N.

5. A compound according to Claim 4 and being R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

6. A compound according to Claim 4 and being R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

7. A compound according to Claim 4 and being R-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

8. A compound according to Claim 4 and being R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid.

9. A compound according to Claim 4 and being R-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

10. A compound according to Claim 4 and being R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-6-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

11. A compound according to Claim 4 and being R-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

12. A compound according to Claim 4 and being R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-8-trifluoromethyl-3-quinolinecarboxylic acid.

13. A compound according to Claim 4 and being R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid.

14. A compound according to Claim 4 and being R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

15. A compound according to Claim 4 and being R-5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

16. A compound according to Claim 4 and being R-1-cyclopropyl-1,4-dihydro-6-fluoro-8-methoxy-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

17. A compound according to Claim 4 and being R-5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

18. A compound according to Claim 4 and being R-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid.

19. A compound according to Claim 4 and being R-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-8-trifluoromethyl-3-quinolinecarboxylic acid.

20. A compound according to Claim 4 and being R-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-7-[3-[1-methyl-1-1(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

21. A compound according to Claim 4 and being R-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid.

22. A compound according to Claim 4 and being R-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid.

23. A compound according to Claim 4 and being R-5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

24. A compound according to Claim 4 and being R-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

25. A compound according to Claim 4 and being R-1-cyclopropyl-8-ethoxy-6-fluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

26. A compound according to Claim 4 and being R-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-8-ethoxy-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

27. The S isomer of claim 3, wherein X is C-H, C-F, C-Cl, C-OCH_3 or N.

28. A compound according to claim 27 and being S-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

29. A compound according to claim 27 and being S-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

30. A compound according to claim 27 and being S-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-6-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

31. A compound according to claim 27 and being S-5-amino-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

32. A compound according to claim 27 and being S-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid.

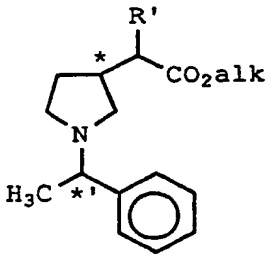
33. A compound according to claim 27 and being S-5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

34. A compound according to claim 27 and being S-5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-[1-methyl-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid.

35. A pharmaceutical composition comprising an antibacterially effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable carrier or diluent.

36. A method of treating bacterial infections comprising administering to a host in need thereof a pharmaceutical composition according to Claim 35.

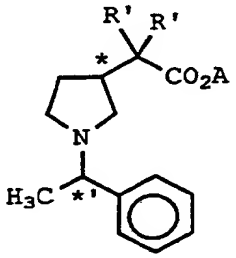
37. A compound of the formula



wherein * and *′ are asymmetric carbon at ms having either the R or S configuration, and R′ and alk are alkyl of 1 to 3 carbon atoms.

38. A compound according to Claim 37, wherein * has the R configuration, and R′ and alkyl are methyl.

39. A compound of the formula

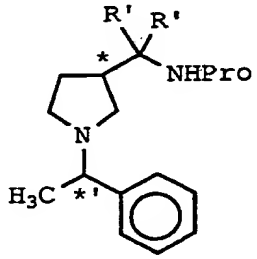


wherein * and *′ are asymmetric carbon atoms having the R or S configurations;

R′ is alkyl of 1 to 3 carbon atoms, and A is hydrogen or alkyl of 1 to 3 carbon atoms.

40. A compound according to Claim 39, wherein * has the R configuration; R′ is methyl, and A is hydrogen or methyl.

41. A compound of the formula

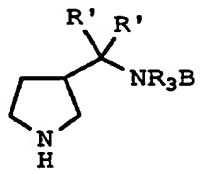


wherein * and *′ are asymmetric carbon atoms having the R or S configurations; R′ is alkyl of 1 to 3 carbon atoms, and Pro is an amino protecting group.

42. A compound according to Claim 41, wherein * has the R configuration, and R′ is methyl.

43. A compound according to Claim 42, wherein Pro is t-butoxycarbonyl.

44. The R or S isomer of the formula

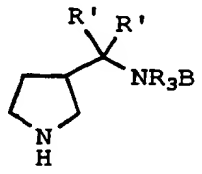


wherein R′ is alkyl of 1 to 3 carbon atoms; R_3 is hydrogen or alkyl of 1 to 3 carbon atoms, and B is hydrogen or an amino protecting group.

45. The R isomer of Claim 44, wherein R′ is methyl and R_3 is hydrogen or methyl.

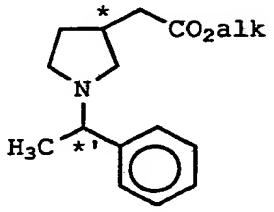
46. The R isomer of Claim 45, wherein B is hydrogen or t-butoxycarbonyl.

47. A process for the preparation of the R or S isomer of a compound of the formula



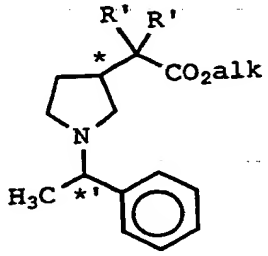
wherein B is hydrogen or an amino protecting group; R_3 is hydrogen or alkyl from 1 to 3 carbon atoms, and R′ is alkyl of 1 to 3 carbon atoms, comprising

(a) dialkylating in a step-wise manner a compound of the formula



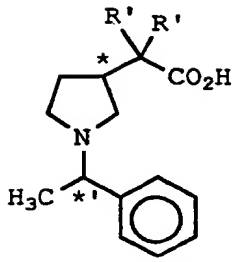
in which alk is alkyl of 1 to 3 carbon atoms and * and *′ are each either of the R or S configuration, and wherein the first alkylation is carried out between -78° and about -50°C, and the second between about -20° and +20°C;

(b) removing the resulting ester of the formula

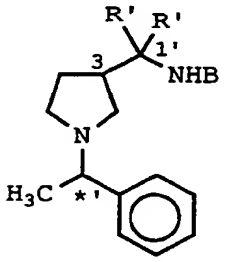


in which R′ is alkyl of 1 to 3 carbon atoms by acid or base hydrolysis;

(c) undergoing the Curtius rearrangement on the resulting acid of the formula



resulting in a compound of the formula

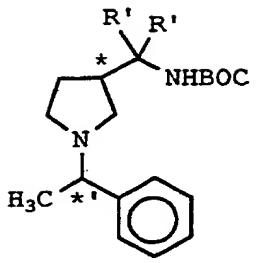


which, if desired, may be alkylated at the 1'-nitrogen by known means, and,

(d) removing the α-methylbenzyl group from the compound of the previous formula to give by catalytic hydrogenation the desired compound.

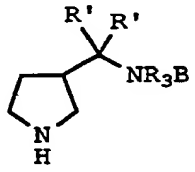
48. The process of Claim 47, wherein the step-wise dialkylation (a) is carried out with lithium diisopropylamide followed by quenching with an alkyl iodide.

49. The process of Claim 47, wherein the Curtius rearrangement (c) is carried out with diphenyl phosphoryl azide in t-butanol to give the compound of the formula

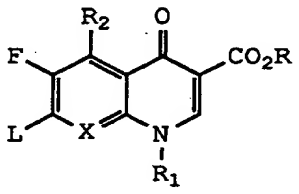


50. The process of Claim 47, wherein catalytic hydrogenation is carried out with hydrogen and palladium on carbon catalyst.

51. A method of using the R and S isomer of the formula

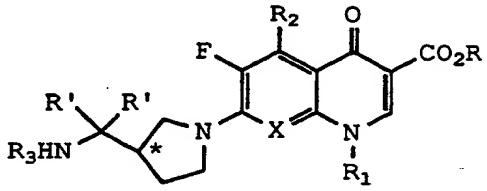


wherein R' is alkyl of 1 to 3 carbon atoms; R_3 is hydrogen or alkyl of 1 to 3 carbon atoms, and B is hydrogen or an amino protecting group which comprises reacting said R or S isomer with a compound of the formula



wherein X is C-H, C-F, C-Cl, C-CF_3, C-OR" or N, in which R" is hydrogen or alkyl of 1 to 3 carbon atoms; R is hydrogen, alkyl of 1 to 3 carbon atoms

or a cation; R_1 is cyclopropyl or 2,4-difluorophenyl; R_2 is hydrogen, methyl or amino, and L is a leaving group and when B is an amino protecting group, removing said group by known means, to provide an antibacterial compound of the formula



or a pharmaceutically acceptable salt thereof, wherein * is an asymmetric carbon atom having the R or S configuration, and R_3 is hydrogen or alkyl of 1 to 3 carbon atoms.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/08422

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 401/04 C 07 D 471/04 C 07 D 207/08
C 07 D 207/09 A 61 K 31/47 A 61 K 31/435

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 401/00 C 07 D 471/00 C 07 D 207/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0207420 (DAIICHI SEIYAKU CO., LTD) 7 January 1987, see claims (cited in the application)	1,3,5
A	US,A,4780468 (WARNER-LAMBERT CO.) 25 October 1988, see claims 1,5,8,16	1,3,5
A	EP,A,0393400 (WAKUNAGA SEIYAKU K.K.) 24 October 190, see page 34, compound 177; page 48, compound 139; claims	1,3,5

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09-03-1992	01.04.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Els Vonk

FURTHER INFORMATION C NTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 36 because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 36 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9108422 SA 54360

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/03/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0207420	07-01-87	AU-B-	589978	26-10-89
		AU-A-	5924586	08-01-87
		JP-A-	62234082	14-10-87
US-A- 4780468	25-10-88	AU-B-	616422	31-10-91
		AU-A-	2006088	09-02-89
		AU-A-	8374391	14-11-91
		EP-A-	0302525	08-02-89
		JP-A-	1066180	13-03-89
		US-A-	4803205	07-02-89
		US-A-	4933335	12-06-90
EP-A- 0393400	24-10-90	AU-A-	5228190	04-10-90
		CN-A-	1045971	10-10-90
		JP-A-	3188074	16-08-91

EPO FORM P0479